## REMARKS

Claims 123-166 constitute the pending claims in the present application. Applicants add new claims 167-172. Support for the subject matter of these claims is found throughout the specification. No new matter has been entered. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note with appreciation that the request for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) is acceptable, and that a CPA has been established.

2-3. Applicants note that the amendments put forth in Paper 45 have been entered in full. Claims 123-166 are pending and under consideration.

4. Claims 123-166 are provisionally rejected under the judicially created doctrine of double patenting over claims 11-13 of copending Application Serial No. 08/462,386. As previously indicated and acknowledged by the Examiner, Applicants will submit a terminal disclaimer, if necessary, upon the indication of allowable subject matter.

5. Claims 165 and 166 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

Applicants contend that the term "neuronal" is defined in the specification, and accordingly one of skill in the art can readily appreciate the meaning of the term. Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more particularly point out that the glial cells are differentiated from neural stem or progenitor cells which are known to give rise to **both** neurons and glia. Support for Applicants' amendments can be found, for example, on page 11, lines 30-36; page 27, lines 8-14; and page 60, lines 13-18. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

6. Claims 123-166 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to enable one of skill in the art to practice the claimed invention. In maintaining this rejection, the Examiner alleges that the specification fails to provide enablement for methods of promoting growth, differentiation, and/or survival of cells other than embryonic cells, and fails to provide enablement for the use of hedgehog polypeptides other than Sonic hedgehog. Applicants respectfully traverse this rejection to the extent it is maintained over the amended claims. Applicants state for the record that Applicants' amendments are made solely to expedite prosecution and to consolidate the issues for Appeal.

Applicants maintain the arguments of record. The specification explicitly contemplates that hedgehog polypeptides can be used to influence not only the behavior of embryonic cells and tissues, but also the behavior of adult cells. In further support of the methods explicitly taught by the application, Applicants have cited post-filing evidence demonstrating that, as taught by the application as filed, hedgehog polypeptides can be used to influence the proliferation, differentiation and survival of adult cells including neuronal cells. Applicants contend that the wealth of post-filing evidence supports the enablement of the claimed subject matter. Simply put, Applicants taught that hedgehog polypeptides **could** be used to influence the behavior of adult cells including neuronal cells, and hedgehog polypeptides **can** in fact be used to influence the behavior of adult cells including neuronal cells. In light of the extensive guidance provided by the specification and the overwhelming evidence in the literature, Applicants maintain that there is no reasonable basis to question the enablement of the claimed subject matter.

For the purpose of consolidating issues for appeal, Applicants will briefly review our understanding of the remaining grounds of rejection. Before discussing the specific issues in this case, Applicants wish to briefly outline, for the record, some of the basic tenets used to evaluate enablement.

MPEP 2164.04 outlines the criteria for evaluating enablement. "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to

those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

The reasoning outlined in MPEP 2164.04 is well supported by case law stating that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

Furthermore, as exemplified by *In re Strahilevitz*, a broadly enabling disclosure need not include a single working example (*In re Strahilevitz*, 668 F.2d 1229, 212 USPQ 561 (CCPA 1982)). In *Strahilevitz*, the court reversed the Appeal Board's holding of non-enablement, and pointed out that the provisions of 35 U.S.C. 112, first paragraph, do not require that Applicants provide working examples. This sentiment was echoed in *In re Wright* which held that to comply with 35 U.S.C. 112, first paragraph, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."

Finally, both the courts and the Board of Patent Appeals and Interferences have issued opinions which recognize that common sense and prosecutorial expediency contradict decisions that would require Applicants to disclose every last detail of an invention. "Not every last detail [of an invention need] be described [in a patent specification], else patent specifications would turn into production specifications, which they were never intended to be." (*In re Gay*, 390 F.2d 769, 774, 135 USPQ 311, 316 (CCPA 1962)). These sentiments were reiterated by the Board in their decision in *Staehelin v Secher*. Citing *In re Gay*, the Board concluded that "the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. 112, first paragraph." (*Staehelin v Secher*, 24 USPQ 2d 1513, 1516 (Bd. Pat. App. & Int. 1992).

Applicants contend that the maintenance of this rejection is contrary to the standards for evaluating enablement outlined in the MPEP, and upheld by the Federal Circuit and the Board of

Patent Appeals and Interferences. For example, despite the guidance provided by the holdings in *In re Marzocchi*, Applicants have gone through the trouble and expense of making of record an extensive array of post-filing evidence which further supports the enablement of the presently claimed methods. This post-filing evidence includes the declarations of Hank Dudek and Lee Rubin, as well as more than a dozen references from the scientific literature that support Applicants' contention that hedgehog polypeptides can be used to influence the proliferation, differentiation, and survival of a number of embryonic **and** adult cell types.

In maintaining the rejection in the face of this substantial post-filing evidence, the Examiner appears to be requiring Applicants to satisfy not merely the standards for enabling the claimed invention, but rather some sort of super-enablement standard that would have required that Applicants provided working examples, in the specification as filed, demonstrating methods of using hedgehog polypeptides in adult neuronal tissue. Clearly, the courts have balked at the notion that Applicants' claims must be limited in scope to only that which is encompassed by the working examples in the specification. Additionally, the very fact that the post-filing evidence supports the prophetic examples disclosed in the specification argues **strongly** against the appropriateness of applying a higher standard than that used in evaluating enablement in cases such as *In re Gay* and *Staehelin v Secher.*

In response to Applicants' arguments of record, the Examiner raises several counter-arguments. Regarding the issue of whether the claims are enabled for methods of promoting growth, differentiation or survival of both embryonic and adult cells, the Examiner has cited a few references in which a hedgehog polypeptide did not influence the fate of a particular neuronal cell type, and has alleged that these examples demonstrate that one of skill in the art must undergo extensive experimentation in order to practice the claimed invention. Once again, Applicants contend that rejecting the claims simply because the Examiner can find particular examples in which Sonic hedgehog polypeptides do not function to promote growth, differentiation, or survival is akin to requiring that Applicants satisfy a standard above and beyond that which is required by the MPEP or under the law.

In accordance with MPEP 2164.05, when making a determination as to the enablement provided for the claimed invention, the evidence must be considered as a whole. Furthermore, "the evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art." (MPEP 2164.05). Applicants contend that this burden has been satisfied.

Furthermore, Applicants point out that even if the claims encompass certain inoperative embodiments, that does not undermine the enablement of the operative subject matter. In accordance with MPEP 2164.08(b), "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." This standard has been upheld in the courts, and permits a claim to encompass a finite number of inoperable embodiments so long as inoperable embodiments can be determined using methodology specified in the application without undue experimentation. See, for instance, *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976).

An additional argument raised by the Examiner concerns whether the claims are enabled for the use of polypeptides comprising variant sequences. The Examiner has pointed to the absence of data regarding the efficacy of non-Sonic hedgehog polypeptides in influencing adult cell types to argue that the effects of hedgehog polypeptides are extremely sensitive to the sequence of the hedgehog polypeptide. However, as previously countered by Applicants, substantial evidence exists to demonstrate that the hedgehog signaling pathway is not as sensitive to sequence variation in the hedgehog protein as the Examiner suggests (see, for example, Chang et al, Pola et al., and Tsuboi and Shults).

These references indicate that Sonic hedgehog polypeptides from one species successfully function in another species despite variations in the sequences of Sonic hedgehog polypeptides derived from each species. The fact that mouse, rat, and human Sonic hedgehog, which vary by approximately 95% at the amino acid level, can function in each animal system contradicts any assertion on the part of the Examiner that biological systems are so sensitive to the sequence of Sonic hedgehog that any use of variant sequences is beyond the level of skill in the art. In fact, given that murine Sonic hedgehog can function in Drosophila, it is clear that the functional activity of Sonic hedgehog is insensitive to a reasonable degree of variability in the amino acid sequence. In maintaining the rejection in the face of such evidence to the contrary, the Examiner is once again inappropriately attempting to limit Applicants to claims directed to subject matter encompassing only the working examples provided in the application.

Given that the presently claimed methods were explicitly contemplated by the specification as filed, and given that the effective use of these methods has been borne out by the

preponderance of the evidence in the field since the filing of this application, Applicants contend that the claims are enabled throughout their scope.

Applicants wish to clarify, for the record, one final point. In the last response, Applicants referred to work performed on other neurotrophic factors to demonstrate that, as of the time of filing, skilled artisans recognized that proteins involved in embryonic development can also have important activities during adult development. Applicants' reference to work performed on other proteins was not meant to indicate or imply a structural relationship between hedgehog polypeptides and the cited neurotrophic factors, but rather to demonstrate that at the time of filing, one of skill in the art appreciated that factors involved in embryonic development could also be used to influence adult cells and tissues. This is an important point because it further illustrates that the extensive experimentation provided in the application as filed using various embryonic model systems, together with the prophetic guidance concerning the use of hedgehog polypeptides to influence adult cells and tissues, is sufficient to enable one of skill in the art to practice the claimed invention.

These references illustrate that, as of the time of filing, skilled artisans appreciated that proteins and signaling pathways involved in embryonic development were also involved in or could influence adult cells and tissues. Furthermore, Applicants contend that this is a basic principle that underlies most scientific research. Biological research is routinely practiced in any of a number of model animal systems including embryonic systems. Embryos derived from mice, rats, frogs, chicks, fish, and flies are used everyday, and these embryonic systems have formed the foundation of cell and developmental biology research for over a century. The use of these embryonic systems provides a faster, cheaper, and more convenient alternative to conducting experiments in adult animals – much in the same way that cell-based in vitro systems are often used instead of animal-based in vivo systems. However, speed and convenience aside, the use of any embryonic or cell-based model system is founded upon a belief that it supplies some reasonable correlation to the adult or the in vivo situation. Otherwise, there would be no benefit to performing even preliminary experimentation in these systems. Unless one wishes to naively argue that the only basis for scientific research is pure inquiry, clearly skilled artisans perform preliminary experimentation in model systems which they believe provide a reasonable correlation to an adult or other in vivo system.

The courts, as well as the New Utility Guidelines for Examination of Patent Applications have addressed the issue of evaluating in vitro evidence with respect to satisfying the requirements under 35 U.S.C. 101, and the principles underlying their analysis are just as applicable to the requirements under 35 U.S.C. 112, first paragraph. (*Cross v Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed Cir. 1985); *In re Brana*, 51 F.3d 1560, 34 USPQ 2d 1436 (Fed. Cir. 1995)).

Applicants maintain that the specification is broadly enabling for methods of influencing embryonic and adult cell fate using hedgehog polypeptides. Applicants further maintain that the specification is broadly enabling for methods using hedgehog polypeptides comprising naturally occurring, as well as variant amino acid sequences. The application explicitly contemplates these methods, and a wealth of post-filing evidence has demonstrated that, as taught in the specification, hedgehog polypeptides influence the growth, differentiation, and survival of embryonic and adult cells. The remaining issues in this case can be summarized with a quotation from *In re Hogan* (*In re Hogan*, 559 F.2d 595, 605-606, 194 USPQ 527, 537 (CCPA 1977)).

> Rejections under 112, first paragraph, on the ground that the scope of enablement is not commensurate with the scope of the claims, orbit about the more fundamental question: To what scope of protection is the applicant's particular contribution to the art entitled?

Applicants contend that the answer to this question is clear. The discovery of vertebrate hedgehog polypeptides and their function in regulating growth, differentiation, and survival of a large number of cell types derived from all three germ layers was a ground-breaking discovery in the fields of cell and developmental biology. That Applicants' prophetic disclosure of the potential roles and uses of hedgehog polypeptides in adult organisms, supported by Applicants' careful analysis of the role of hedgehog during embryonic development, has in fact been subsequently confirmed throughout the scientific and patent literature only serves to further underscore the importance of this invention and of Applicants' broadly enabling disclosure.

Applicants contend that the claims are enabled throughout their scope. Applicants provided a broad disclosure supported by extensive experimentation in embryonic systems, as well as extensive prophetic discussion and direction concerning methods of using hedgehog polypeptides to influence the growth, differentiation, and survival of adult tissues. Applicants respectfully submit that the maintenance of this rejection, and the maintenance of arguments that

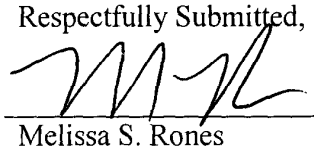
deprive Applicants' claims of any reasonable breadth, is fundamentally unfair. By attempting to limit Applicants to claims directed to methods of using only polypeptides comprising amino acid sequences identical to naturally occurring Sonic hedgehog, as well as claims directed to methods of using these polypeptides only in embryonic cells, Applicants' participation in the patent process is rewarded with claims that offer virtually no meaningful protection. Applicants cannot believe that such protection is the appropriate outcome for this fundamental and critically important scientific advance.

Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter and to consolidate issues for Appeal, Applicants have amended the claims to more explicitly point out specific embodiments of the invention. Applicants' amendments are not in acquiescence to any of the previous grounds of rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. In light of Applicants' amendments and arguments, reconsideration and withdrawal of this rejection are respectfully requested.

## CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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